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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HAYES, ROBERT CLINTON

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,346	STEWARD ET AL.	
	Examiner	Art Unit	
	Robert Clinton Hayes	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-68* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims **1 and 3-13 (each in part)**, drawn to a modified neurotoxin comprising a neurotoxin including a structural modification wherein said structural modification is effective to *enhance* a biological persistence, classified in class 530, subclass 300, for example.

   II. Claims **1, 2, and 4-13 (each in part)**, drawn to a modified neurotoxin comprising a neurotoxin including a structural modification wherein said structural modification is effective to *reduce* a biological persistence, classified in class 530, subclass 300, for example.

   III. Claims **14-28, 31, 32, 34** drawn to a modified neurotoxin comprising a *leucine-based motif*, classified in class 530, subclass 300, for example.

   IV. Claims **29-30, 33** drawn to a modified neurotoxin comprising a *tyrosine-based motif*, classified in class 530, subclass 300, for example.

   V. Claims **35, 36, and 38 (each in part)** drawn to a method for *enhancing* the biological persistence of a neurotoxin wherein a structural modification is fused or added to said neurotoxin and wherein said structural modification comprises a *leucine-based motif*, classified in class 435, subclass 69.1, for example.

   VI. Claims **35, 37, and 38 (each in part)** drawn to a method for *enhancing* the biological persistence of a neurotoxin wherein a structural modification is fused

or added to said neurotoxin and wherein said structural modification comprises a *tyrosine-based motif*, classified in class 435, subclass 69.1, for example.

VII. Claim **39**, drawn to a modified neurotoxin comprising a botulinum type A neurotoxin including a structural modification wherein said structural modification comprises *a deletion of amino acids 1 to 8 and 416 to 437*, classified in class 530, subclass 300, for example.

VIII. Claims **40**, drawn to a modified neurotoxin comprising a botulinum type A neurotoxin including a structural modification wherein said structural modification comprising *substitution of leucine at position 427 for alanine and leucine at position 428 for an alanine*, classified in class 530, subclass 300, for example.

IX. Claims **41, 42, and 44 (each in part)** drawn to a method for *reducing* the biological persistence of a neurotoxin wherein a structural modification is fused or added to said neurotoxin and wherein said structural modification comprises a *leucine-based motif*, classified in class 435, subclass 69.1, for example.

X. Claims **41, 43, and 44 (each in part)** drawn to a method for *reducing* the biological persistence of a neurotoxin wherein a structural modification is fused or added to said neurotoxin and wherein said structural modification comprises a *tyrosine-based motif*, classified in class 435, subclass 69.1, for example.

XI. Claims **45, 47, 48, and 50-56**, drawn to a method of treating a condition comprising a step of administering an effective dose of a modified neurotoxin to a

mammal wherein said neurotoxin contains a *leucine-based motif*, classified in class 514, subclass 2, for example.

XII. Claims **45-47 and 49-56,** drawn to a method of treating a condition comprising a step of administering an effective dose of a modified neurotoxin to a mammal wherein said neurotoxin contains a *tyrosine-based motif*, classified in class 514, subclass 2, for example.

XIII. Claims **57-63, and 66-68 (each in part)**, drawn to a modified neurotoxin comprising a neurotoxin including a structural modification which is effective to *alter a biological activity* wherein the biological persistence of said neurotoxin is *increased*, classified in class 530, subclass 300, for example.

XIV. Claims **57-62, 64, 65, 67, and 68 (each in part)**, drawn to a modified neurotoxin comprising a neurotoxin including a structural modification which is effective to *alter a biological activity* wherein the biological persistence of said neurotoxin is *reduced*, classified in class 530, subclass 300, for example.

2. The inventions are distinct, each from the other because of the following reasons:

3. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive Inventions that are directed to <u>different</u> methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Inventions V, VI, IX, X, XI, and XII are directed to methods that are distinct both physically and functionally, and are not required one for the other.

4. Invention V requires search and consideration of *enhancing* biological persistence of a neurotoxin by introducing a *leucine-based motif*, which is not required by any of the other Inventions. Invention V requires search and consideration of *enhancing* biological persistence of a neurotoxin by introducing a *tyrosine-based motif*, which is not required by any of the other Inventions.

5. Invention IX requires search and consideration of *reducing* biological persistence of a neurotoxin by introducing a *leucine-based motif*, which is not required by any of the other Inventions. Invention X requires search and consideration of *reducing* biological persistence of a neurotoxin by introducing a *tyrosine-based motif*, which is not required by any of the other Inventions.

6. Invention XI requires search and consideration of treating a condition using a neurotoxin comprising a *leucine-based motif*, which is not required by any of the other Inventions. Invention XII requires search and consideration of treating a condition using a neurotoxin comprising a *tyrosine-based motif*, which is not required by any of the other Inventions.

7. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different products, restriction is deemed to be proper because these products constitute patentably distinct inventions for the following reasons. Inventions I, II, III, IV, VII, VIII, XIII, and XIV are directed to products that are distinct both physically and functionally, are not required one for the other, and are therefore patentably distinct. Each of Inventions I, II, III, IV, VII, VIII, XIII, and XIV can be prepared by processes which are materially different each from another, such as by chemical synthesis, or by isolation and purification from natural sources.

8. Inventions V and each of Inventions I, III, and XIII are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the modified neurotoxins of Inventions I, III, and XIII can be prepared by processes which are materially different from the method of Invention V, such as by chemical synthesis, or by isolation and purification from natural sources.

9. Inventions VI and each of Inventions I, IV, and XIII are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the modified neurotoxins of Inventions I, IV, and XIII can be prepared by processes which are materially different from the method of Invention VI, such as by chemical synthesis, or by isolation and purification from natural sources.

10. Inventions IX and each of Inventions II, III, and XIV are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the modified neurotoxins of Inventions II, III, and XIV can be prepared by processes which are materially different from the method of Invention IX, such as by chemical synthesis, or by isolation and purification from natural sources.

11. Inventions X and each of Inventions II, III, and XIV are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the modified neurotoxins of Inventions II, III, and XIV can be prepared by processes which are materially different from the method of Invention X, such as by chemical synthesis, or by isolation and purification from natural sources.

12. Inventions III and XI are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the modified neurotoxin of Invention III can be used in a materially different process of used in materially different processes other than the therapeutic methods of Invention XI such as labeling its target enzymes in a biochemical assay.

13. Inventions IV and XII are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the processes for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the modified neurotoxin of Invention IV can be used in a materially different process of used in materially different processes other than the therapeutic methods of Invention XII such as labeling its target enzymes in a biochemical assay.

14. Inventions I and each of IX, X, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions I and each of IX, X, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions IX, X, XI, and XII do not recite the use or production of the modified neurotoxin with *enhanced* biological persistence of Invention I.

15. Inventions II and each of V, VI, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions II and each of V, VI, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions V, VI, XI, and XII do not recite the use or production of the modified neurotoxin with *reduced* biological persistence of Invention II.

16. Inventions III and each of VI, X, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions III and each of VI, X, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions VI, X, and XII do not recite the use or production of the modified neurotoxin comprising a *leucine-based motif* of Invention III.

17. Inventions IV and each of V, IX, and XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions IV and each of V, IX, and XI are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions V, IX, and XI do not recite the use or production of the modified neurotoxin comprising a *tyrosine-based motif* of Invention IV.

18. Inventions VII and each of V, VI, IX, X, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions VII and each of V, VI, IX, X, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions V, VI, IX, X, XI, and XII do not recite the use or production of the modified neurotoxin comprising a structural modification comprising *a deletion of amino acids 1 to 8 and 416 to 437* of Invention VII.

19. Inventions VIII and each of V, VI, IX, X, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions VIII and each of V, VI, IX, X, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions V, VI, IX, X, XI, and XII do not recite the use or production of the modified neurotoxin comprising a structural modification comprising

substitution of leucine at position 427 for alanine and leucine at position 428 for an alanine of Invention VIII.

20. Inventions XIII and each of IX, X, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions XIII and each of IX, X, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions IX, X, XI, and XII do not recite the use or production of the modified neurotoxin with *altered biological activity* and *increased* biological persistence of Invention XIII.

21. Inventions XIV and each of IX, X, XI, and XII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions of Inventions XIV and each of IX, X, XI, and XII are unrelated product and methods, wherein each is not required, one for another. For example, the claimed methods of Inventions IX, X, XI, and XII do not recite the use or production of the modified neurotoxin with *altered biological activity* and *reduced* biological persistence of Invention XIV.

22. This application contains claims directed to the following patentably distinct species of the claimed invention:

a. Spasmodic dysphonia

b. Laryngeal dystonia

c. Oromandibular dysphonia

d. Lingual dystonia

e. Cervical dystonia

f. Focal hand dystonia

g. Blepharospasm

h. Strabismus

i. Hemifacial spasm

j. Eyelid disorder

k. Cerebral palsy

l. Focal spasticity

m. Spasmodic colitis

n. Neurogenic bladder

o. Anismus

p. Limb spasticity

q. Tics

r. Tremors

s. Bruxism

t. Anal fissure

u. Achalasia

v. Dysphagia

w. Lacrimation

x. Hyperhydrosis

y. Excessive salivation

z. Excessive gastrointestinal secretions

aa. Pain from muscle spasms

bb. Headache pain

cc. Brow furrows

dd. Skin wrinkles

23. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 56 is generic.

24. If applicant selects Invention XI or XII, one species from the condition group must be chosen to be fully responsive.

25. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

26. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

27. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

28. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, separate search requirements, and/or different classification, restriction for examination purposes as indicated is proper.

29. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Robert Clinton Hayes, Ph.D.** whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
September 25, 2003

Gary L. Kunz
GARY KUNZ
SUPERVISORY PATENT EXAMINER
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